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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,505	12/20/2001	Percy Carter	PH-7268	2093

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EXAMINER	
RAO, DEEPAK R	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 06/30/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/027,505	Applicant(s) Carter et al.
	Examiner Deepak Rao	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 13, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above, claim(s) *11-13* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8 and 15-28* is/are rejected.

7) ☒ Claim(s) *9, 10, and 14* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-28 are pending in this application.

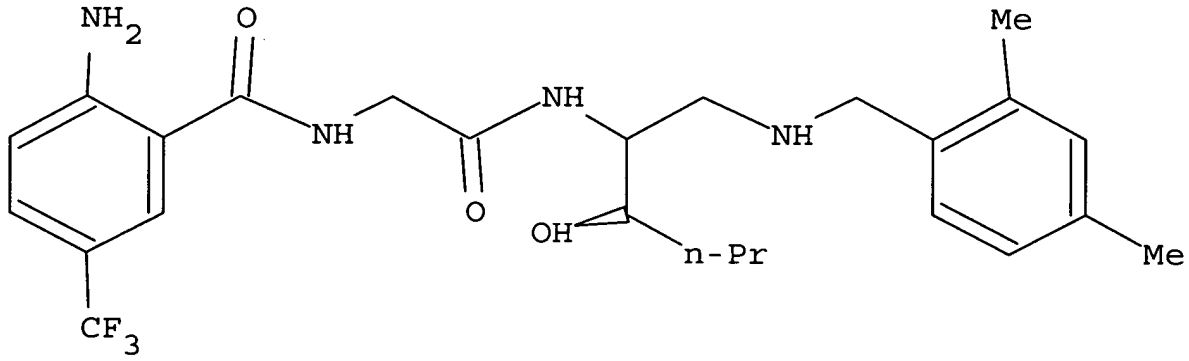
Election/Restriction

Applicant's election with traverse of the species of Example 59, Table 1, page 270 in Paper No. 8 is acknowledged. Applicant indicates that claims 1-10 and 14-28 are readable on the elected species. The traversal is on the ground(s) that the restriction would be improper for the reasons stated in MPEP §803.02, first paragraph. This is not found persuasive because the instant claims do encompass numerous species that have acquired separate status in the art, will support separate patents, and will require different fields of search for the respective inventions. Restriction practice in the case of Markush-type claims is clear from MPEP § 803.02, wherein it is clearly stated that the search and examination of an entire Markush-type claim can be made **when it is not a serious burden** to the examiner. However, in the instant case the instant claims represents multiple number of possibilities based on formula (I) wherein two cyclic groups are linked by a chain which further has varying chain members, all of which further carrying a complex variety of substituent groups. The resulting compounds are not so closely related, they are classified separately, and would support separate patents. Applicant's arguments referring MPEP § 803.02 are fully considered but they were not found to be persuasive for the reasons provided above.

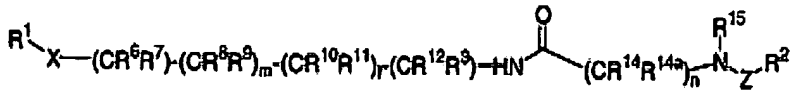
The requirement is still deemed proper and is therefore made FINAL.

Claims 11-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

The elected species of Example 59 is depicted below for convenience:



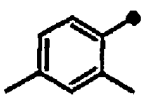
The elected species is compound of formula (I)



(I)

wherein:

R^1 is

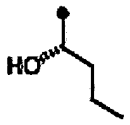


X is -CHR^{16}-NR^{17}- wherein R^{16}, R^{17} are H;

R^6 and R^7 are H;

l and m are 0;

R^3 is $(CRR)_qOH$ wherein R is H, q is 4 **or**



R^{12} is H;

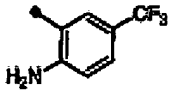
R^{14}, R^{14a} are H;

n is 1;

R^{15} is H;

Z is -C(O)-; and

R^2 is



The guidelines in MPEP § 803.02 provide that upon examination if prior art is found for the elected species, the examination will be limited to the elected species.

Content of MPEP § 803.02 is provided here for convenience:

> As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the non-elected species would be held withdrawn from further

> consideration. As in the prevailing practice, a second action on the merits on the elected claims would be final.
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. **The prior art search, however, will not be extended unnecessarily to cover all nonelected species.** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

The elected species was not found in the prior art and as per the guidelines above, the search was expanded to cover compounds of formula (I) wherein:

R^1 is phenyl substituted with 0-5 R^4;

X is -S-;

R^3 is $(CRR)_rC(O)OR^{3d}$ wherein R is H, r is 1 and R^{3d} is H; and

R^2 is phenyl substituted with 0-5 R^5, retaining all the other variables as indicated for the elected species, and art was found.

Claims 1-10 and 14-28 (all **in part**) wherein the variables are other than those provided herein above (e.g., wherein R^1 and R^2 are heteroaryl system; R^3 and R^{12} together form a cycloalkyl; the species in claim 14 drawn to indol-3-yl, benzodioxol-5-yl, etc.) are withdrawn from further consideration by the examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected species.

Claim Objections

Claim 8 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to the other claims in the alternative only. See MPEP § 608.01(n).

Claim Rejections - 35 U.S.C. § 112

Claims 16-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of rheumatoid arthritis, does not reasonably provide enablement for the treating all other diseases or **preventing** of diseases in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are directed to method of modulation of chemokine receptor activity, or method of treatment of diseases including those associated with HIV infection. However, the specification does not sufficiently establish that the instant compounds can be used in the methods as claimed. The biological test assays are provided in the specification pages 285-289 to determine the *in vitro* MCP-1 antagonistic activity of the compounds and there is insufficient evidence that such studies correlate with *in vivo* efficacy in treatment of all diseases including those associated with HIV in humans. The obstacles to therapy of HIV are well documented in the literature, which include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus; and 2) the complexity and variation of the pathology of HIV infection in

different individuals. Aleman et al. (see the enclosed PubMed Abstract), particularly discloses that "No correlation was seen between MIP-1 alpha or RANTES and any of the parameters" and further, "The biological consequences of the changes in beta-chemokines levels during antiretroviral treatment are still unknown and deserve further studies". Also, Farber (PubMed Abstract enclosed) teaches that non-redundant *in vivo* roles were observed in chemokine gene expressions and further, discloses that "investigations into the roles of chemokines and their receptors in lymphocyte biology will provide information important for understanding the pathogenesis of AIDS and for manipulating immune and inflammatory responses for clinical benefit". Thus it is clear from the above evidence that the ability to treat diseases associated with HIV is highly unpredictable and has met with very little success.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating inflammatory diseases including those associated with HIV infection.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat all types of inflammatory diseases embraced by the instant claims.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders cited, etc. nor there are doses given for the treatment of the disorders recited. The specification provides test procedures (see pages 285-289) to test the compounds *in vitro* and indicates that the compounds of the invention have activity in the antagonism of MCP-1 binding. However, no *in vivo* test procedures or data provided for the compounds commensurate in scope of the claims and there is no disclosure regarding how the *in vitro* results correlate to *in vivo* tests.

6) The breadth of the claims: The instant claims embrace treating or preventing all diseases associated with modulation of chemokine receptor activity, etc., which diseases include those associated with HIV infection.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

The scope of the method claims 19-27 is not adequately enabled solely based on chemokine receptor activity provided in the specification. The instant claims are drawn to 'a method of .... **preventing**...' diseases such as inflammatory diseases, HIV infection, etc., and therefore, the instant claim language embraces disorders not only for the treatment, but for "prevention" which is not remotely enabled. The instant compounds are disclosed have antagonism MCP-1 binding activity and it is recited that the instant compounds are useful in the "prevention" of inflammatory disease, HIV infection, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. The specification provides human eosinophil chemotaxis assay for the inhibition of eosinophilic infiltration to inflammatory sites, which relate to mostly inflammatory mechanism and asthma. Thus, it is inconceivable as to how the claimed compounds can not only treat but also "prevent" a myriad of diseases with different etiologies. For example, a viral disease such as HIV infection has been known to be treated with a nucleoside analog or a protease inhibitor to disrupt the production of viral protein or DNA. (Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements). There is no evidence of record which would enable the skilled artisan

in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 recites the limitation "$(CR'R')_rNR^{7a}C(O)NR^{7a}R^{7a}$, $(CR'R')_rNR^{7a}C(O)O(CR'R')_rR^{7d}$" in the definition of R^5 (page 12, line 17). There is insufficient antecedent basis for this limitation in claim 1 on which claim 8 is dependent. In claim 1, the definition of R^5 includes other variables that are R^{5a}, R^{5d}, etc. and **not** R^{7a} or R^{7d}. The scope of the R^7 variables is different from the R^5 variables.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 15, 19-23 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Ruminski et al., Chem. Abstract 126:264011 (which is the CAPLUS abstract for WO 97/08145). The instantly claimed compounds read on the reference disclosed compounds, see e.g., the compound RN 188804-84-4. The compounds are taught to be useful as pharmaceutical therapeutic agents having antagonism of human vitronectin or $\alpha_v\beta_3$ activity in treating diseases such as arthritis, etc. (see the abstract and page 29 of WO 97/08145*).

**Only relevant pages (1-32) of WO 97/08145 document are enclosed.*

Allowable Subject Matter

Claims 9, 10 and 14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form **to the extent of the examined genus** as indicated above, including all of the limitations of the base claim and any intervening claims.

Claim 8 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to **the extent of the examined genus** as indicated above and to include all of the limitations of the base claim and any intervening claims.

Receipt is acknowledged of the Information Disclosure Statement filed on June 11, 2002 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
Primary Examiner
Art Unit 1624

June 29, 2003